

## **Overview of Vaccine Safety**

### **Importance of Vaccine Safety**

Perhaps the greatest success story in public health is the reduction of infectious diseases resulting from the use of vaccines. Routine immunization has eradicated smallpox from the globe and led to the near elimination of wild polio virus. Vaccines have reduced preventable infectious diseases to an all-time low and now few people experience the devastating effects of measles, pertussis and other illnesses. Prior to approval by the Food and Drug Administration (FDA), vaccines are extensively tested by scientists to ensure that they are effective and safe. Vaccines are the best defense we have against infectious diseases. However, no vaccine is 100% safe or effective. Differences in the way individual immune systems react to a vaccine account for rare occasions when people are not protected following immunization or when they experience side effects.<sup>1,2,3</sup>

As infectious diseases continue to decline, some people have become less interested in the consequences of preventable illnesses like diphtheria and tetanus. Instead, they have become increasingly concerned about the risks associated with vaccines. After all, vaccines are given to healthy individuals, many of whom are children, and therefore a high standard of safety is required. Since vaccination is such a common and memorable event, any illness following immunization may be attributed to the vaccine. While some of these reactions may be caused by the vaccine, many of them are unrelated events that occur after vaccination by coincidence. Therefore, the scientific research that attempts to distinguish true vaccine side effects from unrelated, chance occurrences is crucial. This knowledge is necessary in order to maintain public confidence in immunization programs. As science continues to advance, we are constantly striving to develop safer vaccines and improve delivery in order to better protect ourselves against disease. This overview will focus on vaccine research, how vaccines are licensed, how safety is monitored, and how risks are communicated to the public.<sup>1,2,3</sup>

### **National Childhood Vaccine Injury Act (NCVIA)**

The topic of vaccine safety became prominent during the mid 1970's with increases in lawsuits filed on behalf of those presumably injured by the diphtheria, pertussis, tetanus (DPT) vaccine.<sup>4</sup> Legal decisions were made and damages awarded despite the lack of scientific evidence to support vaccine injury claims.<sup>4</sup> As a result of the liability, prices soared and several manufacturers halted production. A vaccine shortage resulted and public health officials became concerned about the return of epidemic disease. In order to reduce liability and respond to public health concerns, Congress passed the National Childhood Vaccine Injury Act (NCVIA) in 1986. This act was influential in many ways.

1. As a result of the NCVIA, the National Vaccine Program Office (NVPO) was established within the Department of Health and Human Services (DHHS). The responsibility of NVPO is to coordinate immunization-related activities between all DHHS agencies including the Centers for Disease Control and Prevention

- (CDC), Food and Drug Administration (FDA), National Institutes of Health (NIH) and the Health Resources and Services Administration (HRSA).
2. The NCVIA requires that all health care providers who administer vaccines containing diphtheria, tetanus, pertussis, polio, measles, mumps, rubella, hepatitis B, *Haemophilus influenzae* type b and varicella must provide a Vaccine Information Statement (VIS) to the vaccine recipient, their parent or legal guardian prior to each dose. A VIS must be given with every vaccination including each dose in a multi-dose series. Each VIS contains a brief description of the disease as well as the risks and benefits of the vaccine. VISs are developed by the CDC and distributed to state and local health departments as well as individual providers.
  3. The NCVIA also mandates that all health care providers must report certain adverse events following vaccination to the Vaccine Adverse Event Reporting System (VAERS). This system will be described in detail later in the overview.
  4. Under the NCVIA, the National Vaccine Injury Compensation Program (NVICP) was created to compensate those injured by vaccines on a "no fault" basis. This program will be described in detail later in the overview.
  5. The NCVIA established a committee from the Institute of Medicine (IOM) to review the existing literature on vaccine adverse events (health effects occurring after immunization that may or may not be related to the vaccine). This group concluded that there are limitations in our knowledge of the risks associated with vaccines. Of the 76 adverse events they reviewed for a causal relationship, 50 (66%) had no or inadequate research.<sup>1</sup> Specifically, IOM identified the following problems:
    1. limited understanding of biological processes that underlie adverse events
    2. incomplete and inconsistent information from individual reports
    3. poorly constructed research studies (not enough people enrolled for a long enough period of time)
    4. inadequate systems to track vaccine adverse events
    5. few experimental studies published in the medical literature.<sup>1</sup> Significant progress has been made over the past few years to better monitor adverse events and conduct research relevant to vaccine safety.<sup>4,5</sup>

### **Monitoring Vaccine Safety: Pre-licensure**

Before vaccines are licensed by the FDA, they are extensively tested in the laboratory and in human beings to ensure their safety. First, computers are used to predict how the vaccine will interact with the immune system. Then researchers test the vaccine on animals including mice, guinea pigs, rabbits and monkeys. Once the vaccine successfully completes these laboratory tests, it is approved for use in clinical studies by the FDA. During clinical trials, the vaccine is tested on human beings. Participation in these studies is completely voluntary. Many individuals choose to contribute their time and energy for the advancement of science. Informed consent must be obtained from all participants before they become involved in research. This ensures that they understand the purpose of the study, potential risks and are willing to participate. Volunteers agree to receive the vaccine and undergo any medical testing necessary to assess its safety and efficacy.<sup>6</sup>

Vaccine licensure is a lengthy process that may take ten years or longer. The FDA requires that vaccines undergo three phases of clinical trials in human beings before they can be licensed for use in the general public. Phase one trials are small, involving only 20-100 volunteers, and last only a few months. The purpose of phase one trials is to evaluate basic safety and identify very common adverse events. Phase two trials are larger and involve several hundred participants. These studies last anywhere from several months to two years and collect additional information on safety and efficacy. Data gained from phase two trials can be used to determine the composition of the vaccine, how many doses are necessary and a profile of common adverse events. Unless the vaccine is completely ineffective or causes serious side effects, the trials are expanded to phase three which involve several hundred to several thousand volunteers. Typically these trials last several years. Because the vaccinated group can be compared to those who have not received the vaccine, researchers are able to identify true side effects.<sup>1,3,6,7,8</sup>

If the clinical trials demonstrate that the vaccine is safe and effective, the manufacturer applies to the FDA for two licenses, one for the vaccine (product license) and one for the production plant (establishment license). During the application process, the FDA reviews the clinical trial data and proposed product labeling. In addition, the FDA inspects the plant and goes over manufacturing protocols to ensure that vaccines are produced in a safe and consistent manner. Only after the FDA is satisfied that the vaccine is safe is it licensed for use in the general population.<sup>7</sup>

### **Monitoring Vaccine Safety: Post-licensure**

After a vaccine is licensed for public use, its safety is continually monitored. The FDA requires all manufacturers to submit samples from each vaccine lot prior to its release. In addition, the manufacturers must provide the FDA with their test results for vaccine safety, potency and purity. Each lot must be tested because vaccines are sensitive to environmental factors (like temperature) and can be contaminated during production. During the last ten years, only three vaccine lots have been recalled by the FDA. One lot was mislabeled and another was contaminated with particles during production. A third lot was recalled after the FDA discovered potential problems with the manufacturing process at a production plant.<sup>7</sup>

While clinical trials provide important information on vaccine safety, the data are somewhat limited because of the small number (hundreds to thousands) of study participants. Rare side effects and delayed reactions may not be evident until the vaccine is administered to millions of people. Therefore, the Federal Government has established a surveillance system to monitor adverse events that occur following vaccination. This project is known as the Vaccine Adverse Events Reporting System (VAERS). More recently, large-linked databases (LLDBs) containing information on millions of individuals have been created in order to study rare vaccine side effects.<sup>1,3</sup>

### **Vaccine Adverse Event Reporting System (VAERS)**

The National Childhood Vaccine Injury Act of 1986 mandated that all health care providers report certain adverse events that occur following vaccination. As a result, the Vaccine Adverse Events Reporting System (VAERS) was established by the FDA and the Centers for Disease Control and Prevention (CDC) in 1990. VAERS provides a mechanism for the collection and analysis of adverse events associated with vaccines currently licensed in the United States. Adverse events are defined as health effects that occur after immunization that may or may not be related to the vaccine. VAERS data are continually monitored in order to detect previously unknown adverse events or increases in known adverse events.<sup>1,9</sup>

Approximately 10,000-12,000 VAERS reports are filed annually, with 20% classified as serious (causing disability, hospitalization, life threatening illness or death).<sup>1</sup> Anyone can file a VAERS report including health care providers, manufacturers, vaccine recipients or, when appropriate, parents/guardians. Those who have experienced an adverse reaction following immunization are encouraged to seek help from a health care professional when filling out the form. VAERS forms can be obtained in several ways. Each year the form is mailed to more than 200,000 physicians specializing in pediatrics, family practice, internal medicine, infectious diseases, emergency medicine, obstetrics and gynecology. In addition, copies are sent to health departments and clinics that administer vaccines. The VAERS form requests the following information: the type of vaccine received, the timing of vaccination, the onset of the adverse event, current illnesses or medication, past history of adverse events following vaccination and demographic information about the recipient (age, gender, etc.). The form is pre-addressed and stamped so it can be mailed directly to VAERS. To request a VAERS form or assistance in filling in out, call 1-800-822-7967.<sup>1,9</sup>

A contractor, under the supervision of FDA and CDC, collects the information and enters it into a database. Those reporting an adverse event to VAERS receive a confirmation letter by mail indicating that the form was received. This letter will contain a VAERS identification number. Additional information may be submitted to VAERS using the assigned identification number. Selected cases of serious adverse reactions are followed up at 60 days and one year post-vaccination to check the recovery status of the patient. The FDA and CDC have access to VAERS data and use this information to monitor vaccine safety and conduct appropriate research studies. VAERS data (minus any personal information) is also available to the public.<sup>1,9</sup>

While VAERS provides useful information on vaccine safety, the data are somewhat limited. Specifically, judgments about causality (whether the vaccine was truly responsible for an adverse event) cannot be made from VAERS reports because of incomplete information. VAERS reports often lack important information such as laboratory results. As a result, researchers have turned more recently to large-linked databases (LLDBs) in order to study vaccine safety. LLDBs provide scientists with access to the complete medical records of millions of individuals receiving vaccines (all identifying information is deleted to protect the confidentiality of the patient). One example of a LLDB is the Vaccine Safety Datalink (VSD) project described below,

which is coordinated by the CDC. Studies conducted using LLDBs, like the VSD, are also known as post-marketing research or phase four clinical trials.<sup>1</sup>

### **Vaccine Safety Datalink (VSD) Project**

The gaps that exist in the scientific knowledge of rare vaccine side effects prompted the CDC to develop the Vaccine Safety Datalink (VSD) project in 1990. This project involves partnerships with seven large health maintenance organizations (HMOs) to continually monitor vaccine safety. VSD is an example of a large-linked database (LLDB) and includes information on more than six million people. All vaccines administered within the study population are recorded. Available data include vaccine type, date of vaccination, concurrent vaccinations (those given during the same visit), the manufacturer, lot number and injection site. Medical records are then monitored for potential adverse events resulting from immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypotheses. At present, the VSD project is examining potential associations between vaccines and a number of serious conditions. The database is also being used to test new vaccine safety hypotheses that result from the medical literature, VAERS, changes in the immunization schedule or from the introduction of new vaccines. This project is a powerful and cost-effective tool for the on-going evaluation of vaccine safety.<sup>1,10</sup>

### **Vaccine Injury Compensation Program**

In order to reduce the liability of manufacturers and health care providers, the National Childhood Vaccine Injury Act of 1986 established the National Vaccine Injury Compensation Program (NVICP). This program is intended to compensate those individuals who have been injured by vaccines on a "no-fault" basis. No fault means that people filing claims are not required to prove negligence on the part of either the health care provider or manufacturer to receive compensation. The program covers all routinely recommended childhood vaccinations. Settlements are based on the Vaccine Injury Table which summarizes the adverse events caused by vaccines. This table was developed by a panel of experts who reviewed the medical literature and identified the serious adverse events that are reasonably certain to be caused by vaccines. Examples of table injuries include anaphylaxis (severe allergic reaction), paralytic polio and encephalopathy (general brain disorder). The Vaccine Injury Table was created to justly compensate those injured by vaccines while separating out unrelated claims. As more information becomes available from research on vaccine side effects, the Vaccine Injury Table is updated.<sup>11,12</sup>

Individuals and their families can qualify for compensation in three ways. First, is to show that an injury found on the Vaccine Injury Table occurred in the appropriate time interval following immunization. The other two ways to qualify include proving that the vaccine caused the condition or demonstrating that the vaccine worsened or aggravated a pre-existing condition.<sup>11,12</sup>

The vaccine injury compensation process begins when an individual files a petition with the United States Court of Federal Claims. At that point, a physician from the program reviews the petition to determine whether it meets the criteria for compensation. This recommendation is not binding. A Court attorney then reviews the case and makes an initial decision for or against entitlement to compensation. Decisions may be appealed to the Court of Federal Claims, and then to the Federal Circuit Court of Appeals. This process occurs at no cost to the individual filing the claim. NVICP is coordinated by the Department of Health and Human Services and the Department of Justice. For more information on the program or for assistance in making a claim, call 1-800-338-2382.<sup>11,12</sup>

### **Improvements in Vaccine Safety**

In the last decade, numerous changes in vaccine production and administration have reduced the number of adverse events and resulted in safer vaccines. A more purified acellular pertussis (aP) vaccine has been licensed for use and has replaced the whole-cell pertussis vaccine used in DTP (diphtheria, tetanus, pertussis vaccine). Several studies have evaluated the safety and efficacy of DTaP as compared to DTP and have concluded that DTaP is effective in preventing disease and that mild side effects and serious adverse events occurred less frequently when the DTaP vaccine was given.<sup>3</sup> Recent changes in the schedule of polio vaccines have also resulted in fewer reports of serious side effects. In 1997, the Advisory Committee on Immunization Practice recommended a change in the vaccination schedule to include sequential administration of inactivated polio vaccine (IPV) and oral polio vaccine (OPV).<sup>13</sup> This sequential schedule was expected to produce a high level of individual protection against the disease caused by wild polio virus, while reducing by 50 to 70% vaccine-associated paralytic polio (VAPP) that occurs in 8-10 people a year who receive OPV.<sup>14</sup> Today, only IPV is on the recommended childhood immunization schedule.

### **Risk Communication**

At some point, almost every person in the United States is vaccinated. Therefore, many individuals question how vaccines are made, if they are effective and whether they are safe.<sup>15</sup> People seek answers to these questions from a wide variety of sources including family, friends, health care providers, the Internet, television and medical literature. The information they receive is complex and, at times, inaccurate or misleading. Therefore, health professionals have a responsibility to provide accurate, understandable information and to handle vaccine safety concerns appropriately. As mentioned previously, the NCVIA requires all health care providers who administer vaccines to discuss the potential risks and benefits of immunization. In these situations, risk communication is a necessary skill.<sup>1</sup>

Risk communication involves a dynamic exchange of information between individuals, groups and institutions. This information must acknowledge and define the risks associated with vaccination in a way the public can understand. This is difficult given the current environment where few people experience the devastation of vaccine-preventable

diseases. It is further complicated by the fact that immunization is associated with some degree of personal discomfort when needles are used to administer vaccines.<sup>1</sup>

In 1996, the Institute of Medicine's Vaccine Safety Forum held a workshop on risk communication and vaccination. Three key concepts emerged:

"First, risk communication is a dynamic process in which many participate, and these individuals are influenced by a wide variety of circumstances, interests, and information needs. Effective risk communication depends on the providers' and recipients' understanding more than simply the risks and benefits; background experiences and values also influence the process."<sup>18</sup> Good risk communication recognizes a diversity of form and context needs in the general population.

Second, the goal that all parties share regarding vaccine risk communication should be informed decision making. Consent for vaccination is truly 'informed' when the members of the public know the risks and benefits and make voluntary decisions.

Finally, there is often uncertainty about estimates of the risk associated with vaccination. Risk communication is more effective when this uncertainty is stated and when the risks are quantified as much as science permits. Trust is a key component of the exchange of information at every level, and overconfidence about risk estimates that are later shown to be incorrect contributes to a breakdown of trust among public health officials, vaccine manufacturers, and the public. Continued research to improve the understanding of vaccine risks is critical to maximizing mutual understanding and trust."<sup>19</sup>

Several resources are available to address the risks and benefits of vaccination. Federal law requires all health care providers who administer vaccines in the United States to provide Vaccine Information Statements (VISs) to vaccine recipients (or their parent/guardian) prior to each dose being administered. VISs are developed by CDC and contain information on the disease as well as the risks and benefits associated with immunization. These documents, and others, can be obtained from the National Immunization Hotline 1-800-232-2522 or from the [National Immunization Program's Web Page](#).

## **Conclusion: The Future of Vaccine Safety**

The importance of vaccine safety will continue to grow throughout the twenty-first century. The development and licensure of new vaccines will add to the already complicated immunization schedule. Scientists may also perfect new ways of administering immunizations including edible vaccines and needleless injections. However they are formulated or delivered, vaccines will remain the most effective tool we possess for preventing disease and improving public health in the future.

## **Additional Information**

### **General Vaccine Safety**

- [Epidemiology and Prevention of Vaccine-Preventable Diseases, Vaccine Safety \(Chapter 15\)](#)
- [Vaccine Safety: Current and Future Challenges](#)
- [Vaccine Safety Resource List](#)
- [Institute of Medicine, Vaccine Safety Forum \(1997\)](#)
- [World Health Organization's Web Page on Vaccine Safety](#)
- [National Vaccine Program Office's Web Page on Vaccine Safety](#)
- [Enhancing Vaccine Safety](#)

### **Vaccine Adverse Events**

- [Institute of Medicine, Adverse Effects of Pertussis and Rubella Vaccines \(1991\)](#)
- [Institute of Medicine, Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality \(1994\)](#)

### **Vaccine Licensure**

- [FDA Licensure of Vaccines](#)

### **Monitoring Vaccine Safety**

- [The Complicated Task of Monitoring Vaccine Safety](#)

### **The Vaccine Adverse Events Reporting System (VAERS)**

- [The Vaccine Adverse Events Reporting System \(VAERS\)](#)
- [FDA's Web Site on VAERS](#)
- [VAERS Table of Reportable Events](#)
- [VAERS Form](#)

### **The Vaccine Safety Datalink (VSD) Project**

- [Vaccine Safety Datalink Project: Current and Completed Studies](#)
- [Vaccine Safety Datalink References](#)
- [Vaccine Safety Datalink Project: A New Tool for Improving Vaccine Safety Monitoring in the United States](#)

### **National Vaccine Injury Compensation Program (NVICP)**

- [NVICP's Web Site](#)

### **Risk Communication**

- [Institute of Medicine, Risk Communication and Vaccination \(1997\)](#)
- [Current Vaccine Information Statements \(VISs\)](#)
- [Instructions for Vaccine Information Statements \(VISs\)](#)



- JAMA article: [Content and Design Attributes of Antivaccination Web Sites](#)

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